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A Summary of Important Documents in the Field of Research Ethics

Bernard A. Fischer IV[1,2]

[2]Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, P.O. Box 21247, Baltimore, MD, 21228

Today's researchers are obligated to conduct their studies ethically. However, it often seems a daunting task to become familiar with the important ethical codes required to do so. The purpose of this article is to examine the content of those ethical documents most relevant to the biomedical researcher. Documents examined include the Nuremberg Code, the Declaration of Helsinki, Henry Beecher's landmark paper, the Belmont Report, the U.S. Common Rule, the Guideline for Good Clinical Practice, and the National Bioethics Advisory Commission's report on research protections for the mentally ill.

Key words: Beecher/Belmont Report/Common Rule/Declaration of Helsinki/ethics/National Bioethics Advisory Commission/Nuremberg Code

Introduction

The last 2 centuries have witnessed enormous strides in the advancement of medicine. More influential than available technology has been the very technique of science itself. The scientific method and careful observation have given us a way of making sense of disease. Clinical trials, a relatively recent advance in the practice of medicine, have allowed evaluation of treatments. Medical ethics should be viewed along these same lines: as an evolution of technique meant to sharpen our results and benefit humankind.

The purpose of this article is to help the researcher make sense of major documents in the field of medical ethics as they pertain to work with human subjects. These important documents will be discussed in brief historical context and then summarized.

[1]To whom correspondence should be addressed; phone: 410-402-7548, fax: 410-402-7198, e-mail: bfisc001@umaryland.edu.

The Nuremberg Code

During World War II the Axis Powers did a great deal of human experimentation. Both Imperial Japan and Nazi Germany subjected human beings to torturous ordeals in order to obtain data that might prove useful in their war effort.[1–2] When the Allies were victorious in Asia, the U.S. government made a secret deal with Japanese scientists. In return for use of Japanese data, the United States would shield these scientists from prosecution.[1] This was not the case in Europe. Distrust between the Soviet Union and the Allies forced much of the aftermath of the Nazi regime into the public eye. Many Nazi scientists were openly tried for war crimes. These trials were held in Nuremberg, Germany—at the time 1 of the only cities in the country with a standing court building.

Issued by the Nuremberg Military Tribunal in 1947, the Nuremberg Code is a 10-point statement meant to prevent future abuse of human subjects.[2] It states that, above all, participation in research must be voluntary. The other points are as follows:

- The results of the research must be useful and unobtainable by other means.
- The study must be rationally based on knowledge of the disease or condition to be studied.
- It must avoid unnecessary suffering.
- The study cannot include death or disabling injury as a foreseeable consequence.
- Its benefits must outweigh its risks.
- The study must use proper facilities to protect participants.
- The study must be conducted by qualified individuals.
- Participants may withdraw from the study if they wish.
- Investigators must be prepared to stop the study should participants die or become disabled as a result of participation.

The Nuremberg Code was created by opining on the testimony of physician witnesses and was said to represent current thoughts on the topic of human experimentation.[2] Although intended to refer to this particular trial and never formally adopted by any state or international agency, the Nuremberg Code has been tremendously influential—becoming the basis of later documents that are highly relevant to research today.

The Declarations of Geneva and Helsinki

Organized in 1945, the World Medical Association (WMA) took the place of l'Association Professionnelle Internationale des Médecins—an international medical association that had been effectively disbanded during World War II. Physicians from the WMA were appalled at the atrocities revealed at the Nuremberg Trial and, in 1949, issued a code of medical ethics to condemn what Nazi doctors had done. This code came to be known as the Declaration of Geneva for the city in which it was officially adopted. In it, the WMA laid out general principles to which physicians should hold themselves. For example, "the health of my patients will be my first consideration."[3(p 1)] Despite the noble goals of the Declaration of Geneva, its vague language did not allow accurate interpretations in the newly emerging field of medical ethics. To clarify a physician's duties as an investigator, the WMA began reexamining the issue in 1953. The subject was discussed and debated for several years before the resulting document, *Ethical Principles for Medical Research Involving Human Subjects*, was approved in 1964.[3] Again taking its name from the city in which it was adopted, this paper became known as the Declaration of Helsinki.

Beginning in 1975, the Declaration of Helsinki has been revised several times—most recently in 2000. Minor clarifications were also added in 2002 and 2004. Its current form contains 3 sections in 32 separate paragraphs—each on a specific topic.

Section A sets the stage of what human research is and why it is necessary and stresses the obligation of the physician to prioritize participant health. This section reminds physicians that special populations involved in research must be closely monitored. Examples of these special populations are the "economically and medically disadvantaged," those who cannot give informed consent (or who may be doing so "under duress"), those who will not benefit personally from the research, and those for whom "research is combined with care."

Section B discusses basic principles for medical research and reaffirms points of the Nuremberg Code—such as the need for basing a human trial rationally on available evidence. However, the Declaration of Helsinki expands the Nuremberg principle of voluntarism significantly. It states that potential subjects should only give consent after being fully informed of the study's setup, goals, and sources of funding; potential conflicts of interest; researcher affiliation(s); risks and benefits; and their right to withdraw (see table 1). Only populations likely to benefit from the research should be targeted for recruitment, and vulnerable populations should not be used when other populations are available and appropriate. Furthermore, populations requiring a third party to give informed consent (because they are unable) should give assent instead (thereby agreeing to participate even if not able to be fully informed). In all cases of obtaining consent, a researcher should be mindful of unduly influencing a patient by way of a clinical relationship.

Section C discusses research combined with medical care and states that research can only be combined with clinical care if it has the potential to prophylax, diagnose, or treat. In these cases, subjects must be made aware what aspects of their care are experimental. Experimental care may be offered to individuals outside a formal research study if standard care has been ineffective for their condition. Section C also contains the 2 most controversial statements in the document: Paragraphs 29 and 30.

Paragraph 29 asserts that new treatments should be tested against standard treatment; thus proscribing the use of placebo-controlled studies when a known treatment exists. This statement was clarified to allow exceptions in cases where a placebo is "scientifically" necessary to evaluate a treatment or when the condition being investigated is "minor" and a placebo does not entail additional risks to the subject. Paragraph 30 states that, at study conclusion, all participants should be assured access to the "best" treatment as identified in the study. It is not the purpose of this article to debate the pros and cons of these statements, but it should be obvious that well-intentioned and informed investigators could come to conclusions different than those allowed by Paragraphs 29 and 30 in the Declaration of Helsinki. (For further reading on this debate, see [4–8].)

The Beecher Paper

Henry K. Beecher was a professor of anesthesiology engaged in human research at Harvard's Massachusetts General Hospital. Dr. Beecher had followed the Nuremberg Trials very closely and was appalled at the similarities between what Nazi scientists had done and what some researchers in America seemed to be doing. He especially objected to experiments that seemed to exploit participants—some from vulnerable populations. He began publishing articles and lecturing to draw attention to the topic. The best known of these essays is the 1966 *New England Journal of Medicine* special article entitled "Ethics and Clinical Research."[9]

Beecher focused this article on exposing studies done to expand scientific knowledge showing little concern for how subjects would fare. For example, 1 study he cites was designed to determine whether the central nervous system or the cardiovascular system would collapse first. Patients' blood pressures were decreased from a mean of 109 to a mean of 48 mmHg. The investigators noted cerebral ischemia before the onset of cardiac problems, thus determining that the nervous system was more sensitive. But what of the subjects whose brains were made deliberately hypoxic for the duration of the experiment? Another experiment involved giving cirrhotic patients loads of nitrogen to induce hepatic encephalopathy. The conclusion

Table 1. Elements of Informed Consent Required by Various Documents

Elements of Informed Consent Required	Declaration of Helsinki	Belmont Report	Common Rule	Council for International Organizations of Medical Sciences Guidelines	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use "Guideline for Good Clinical Practice"
Identification of Study as Research			+		+
Description	+	+	+	+ (emphasizing difference versus clinical care)	+
Duration			+	+	+
Goals	+	+	+		+
Risks/Benefits	+	+	+	+	+
Right to Withdraw	+	+		+	
Potential Conflicts of Interest	+				
Funding Sources	+			+	
Researcher Affiliation	+				
Alternative Procedures		+	+		+
Contact Name			+		+
Emphasis on Voluntarism			+	+	+
Limits of Compensation			+	+	+
Number of Subjects to Be Recruited					+
Subject's Responsibilities/Expenses					+
Institutional Review Board/ Independent Ethics Committee Has Access to Records					+
Steps Ensuring Privacy				+	+
Definitions				+	
Rights to Access Results				+	
Opportunity to Ask Questions		+			

of that experiment was "administration of these substances to patients with cirrhosis may be hazardous."[9(p1358)]

The more well known of Beecher's examples include injecting mentally retarded children with hepatitis to ascertain the period of infectivity, injecting convalescents with cancer cells, and the transplant of a melanoma from a woman to her mother (both of whom subsequently died of metastatic melanoma). In the hepatitis example, specifically, it was clear that mentally retarded children were used as a matter of administrative convenience and not because the research was meant to benefit them in any way.

Beecher concludes by saying that, just as U.S. courts reject evidence obtained unconstitutionally—even if it is useful in the pursuit of justice—journal editors should reject papers with information obtained unethically. The idea that medical journal editors are a final common pathway in the evaluation of a study's ethics was later adopted by the International Committee of Medical Journal Editors—known as the Vancouver Group.

The Vancouver Group

The International Committee of Medical Journal Editors was originally and is still best known as the Vancouver Group—after the location of its first meeting. The group initially met in 1978 to discuss issues of format, such as a uniform way to cite references. However, it soon began addressing the many ethical issues in the medical journal business.

The group publishes the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, which was completely revised in 1997 and updated in 1999, 2000, and 2001. In 2003, official statements of the group were incorporated into the *Uniform Requirements*, resulting in the current, 2004, edition.[10]

The *Uniform Requirements* consists of 9 sections, only the second of which is relevant for this discussion. The second section, entitled "Ethical Considerations in the Conduct and Reporting of Research," is broken into 6 subsections: authorship, editorial obligations, peer review, conflicts of interest, privacy and confidentiality, and human/animal protections. This article will focus on the last 3 of these subsections.

Conflicts of interest are defined in the realm of relationships. Whether a researcher has financial support from a pharmaceutical company or is a close friend of a pharmaceutical company executive, either relationship may cast suspicion on the results of a study using that company's product. The *Uniform Requirements* recognizes that these relationships do not necessarily result in ethical problems, only that they *may* indicate a potential for biased results. This potential conflict of interest is dealt with by having authors reveal any "relationships that might bias their work."[10(p4)]

Regarding privacy and confidentiality, participants in studies should not be identifiable in the resulting article. If there is a potential for identification—through a photo or pedigree and so on—the individual should be shown the article and asked for consent to publish.

The Vancouver Group requires that if humans participated in a study, the authors must report whether they conducted the research in accordance with local ethical review standards and the Declaration of Helsinki. This paragraph may become problematic in the sense that many studies given Institutional Review Board (IRB) approval may not have been examined under the Declaration of Helsinki. In fact, most U.S. IRBs work under federal regulations known as the "Common Rule" and not Helsinki. Authors may then incorrectly report that they have been in accordance with Helsinki when they have not. This does not imply that these studies are unethical—only that some of the more controversial statements of Helsinki may not, in fact, have been addressed.

The Belmont Report

In 1974, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created for the U.S. Department of Health, Education, and Welfare (DHEW—now known as the Department of Health and Human Services after a separate Department of Education was established in 1979). The commission's charge was to identify ethical principles underlying research and develop guidelines for respecting these principles. Although acknowledging the existence of other codes governing human research, the commission thought that other codes amounted to lists of regulations that might not allow the resolution of complex ethical questions. The commission postulated that looking at the topic more generally would allow recognition of fundamental principles. Researchers could then appeal to these principles to resolve dilemmas for which other codes have no answer.

The report, issued in 1979, is entitled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*.[11] It came to be known as the Belmont Report, after the Smithsonian Institution's Belmont Conference Center (where most of the meetings of the commission took place). The commission concluded that the primary principles underlying ethical research with human beings are respect for persons, beneficence, and justice. The methods used to recognize these principles are informed consent, risk/benefit analysis, and appropriate selection of patients.

Informed Consent

Informed consent requires that information be shared with a potential subject, that he or she comprehend the information given, and that the person voluntarily agree to participate in the research. Information shared should "generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research"[11(p5)] (see also table 1). The report leaves the assessment of comprehension up to the researcher but does stipulate that a written or oral test may be required depending on the nature of the risks involved.

The report notes that there are special classes of potential subjects in whom comprehension may be limited. These patients include children, the "mentally disabled," the terminally ill, and the comatose—who must also be given the opportunity to assent to the research if they are able ("unless the research entails providing them with therapy unavailable elsewhere").[11(p6)] However, to protect the interests of these vulnerable populations, a third party should give consent to the study. This third party should be someone "most likely to understand the incompetent subject's situation and to act in that person's best interest."[11(p6)]

Another component of informed consent is the voluntariness of the decision to participate. The commission recognized that flat-out coercion involving threats of harm are not the only way to affect a patient's voluntariness—"undue influence" is also disallowed. This inappropriate influence is offering "excessive, unwarranted, inappropriate, or improper reward" but also pressure coming from a position of power "to obtain compliance."[11(p6)] Recognizing a fine line between "justifiable persuasion" and "undue influence," the commission notes that denial of clinical treatment to those not participating in a trial is an example of the latter.

Risks and Benefits

Assessment of risks and benefits begins by determining the soundness of the research design. Next, risk is discussed in both the probability that a harm will occur and "the severity of the envisioned harm."[11(p7)] Benefits are likewise discussed. It is pointed out that, compared to risks, benefits are more amenable to generalization. Studies could benefit a patient group, "society," and/or "scientific knowledge." Recognizing that there is as yet no perfect means of doing so, the committee recommends that risks and benefits be studied by a "systematic, nonarbitrary analysis." Caveats are that no "brutal or inhumane treatment of human subjects" could ever be justified and only risks necessary to achieve the experimental ends should be tolerated.[11(p7)]

Selection of Participants

In patient selection, the principle of justice is cited most often. This means, more or less, treating equals equally—therefore, people with the same illness should be offered research participation equally (or maybe bear the risks of research equally?). However, in the interest of fairness, people should not be used for research simply as a matter of "administrative convenience " (see the section on the Beecher article). Therefore, classes of people like prisoners or "the mentally infirm" may be invited to participate in research "only on certain conditions" (which the report declines to specify).[11(p7)]

The Common Rule

In addition to establishing the Belmont Commission for the DHEW, the National Research Act of 1974 established a set of guidelines for research with human subjects. These regulations introduced the concept of the IRB to the process of research funded by the DHEW. Regulations were added in 1978 to specifically address research with pregnant women, fetuses, and in vitro fertilization as well as research with prisoners. In 1983 regulations were added to address research with children. After several years of debate and examination, it was proposed that all federally connected research come under a single set of regulations. Thus, in 1991, the regulations of the DHEW—now the Department of Health and Human Services (DHHS)—became a "Common Rule" for 16 federal agencies (the Departments of Health and Human Services, Agriculture, Energy, Commerce, Housing and Urban Development, Justice, Defense, Education, Veterans Affairs, and Transportation and the National Aeronautics and Space Administration, the Consumer Product Safety Commission, the Agency for International Development, the Environmental Protection Agency, the National Science Foundation, and the Central Intelligence Agency).[12]

The Common Rule is technically Subpart A, Part 46: Protection of Human Subjects, of Title 45: Public Welfare, in the Code of Federal Regulations (46 CFR 45). Subparts B, C, and D of 46 CFR 45 are also relevant to this discussion. Subpart A is "basic policy for protection of human research subjects." Subpart B is the "additional protection for pregnant women, human fetuses, and neonates involved in research." Subpart C is the "additional DHHS protection pertaining to biomedical and behavioral research involving prisoners as subjects." Subpart D is the "additional DHHS protection for children involved as subjects in research."

Basic Policy

In general, any research conducted by or for any of the 16 federal agencies mentioned above—including research supported by any of the agencies—is governed by this policy. The Common Rule also applies to research subject to oversight by any of the agencies, even if not directly supported by them (e.g., private industry pharmaceutical research, since their products are ultimately governed by the Food and Drug Administration).

Certain terms are defined in the policy—including the well-known determination of "minimal risk." Risk is minimal when the "probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (§46.102[i]).

IRBs are also described in the policy:

- Every IRB must have a minimum of 5 members.
- The members must have varying backgrounds, with no IRB made up of a single profession.
- The IRB must have men and women members.
- The IRB should represent different races, cultural backgrounds, and "community attitudes" (§46.107[a]).
- Of the members, at least 1 should be totally independent of the institution; 1, chiefly concerned with science; and 1, chiefly concerned with areas other than science.
- Each IRB must have enough space and staff to meet regularly and function adequately.
- All IRB members must be listed for the federal government with their degrees, relevant experience, and relationship to the institution hosting the IRB.
- The IRB must have written procedures for scheduling initial reviews of research projects, for the frequency of monitoring ongoing projects, and for researchers to report newly determined risks or harms not originally reviewed by the board.
- For the IRB to convene, a simple majority of members needs to be present—although a member chiefly concerned with areas other than science must always be in attendance.

The charge of each IRB is to evaluate the risk/benefit ratio of proposals, selection of subjects, and protection of subjects' confidentiality. The IRB assures that potential subjects will be informed about the research prior to their consent being sought and that the consent is documented.

The components of an informed consent per the Common Rule include an identification of the project as research, its purpose, and its duration; a description of the procedure, risks/benefits, and possible alternatives to participation; information on who to contact with questions or if injury were to occur (as well as the limits of compensation provided by the researchers); and assurance that participation is voluntary (see table 1). Other areas that may be included in informed consent at the discretion of the IRB are acknowledgment that the research may pose a risk "currently unforeseeable" (e.g., to a fetus if the women were to become pregnant), the fact that the researcher may remove the participant from the study against the participant's wishes, and the "number of subjects involved in the study" (§46.116[b]). The informed consent process may be modified or even waived by the IRB provided the research is "minimal risk," the waiver would not "adversely affect the rights and welfare of subjects," "the research could not practicably be carried out without the waiver or alteration," *and* "whenever appropriate, the subjects will be provided with additional pertinent information after participation" (§46.116[d]).

Pregnant Women, Fetuses, and Neonates

Subpart B of 46 CFR 45 affords special protections to pregnant women, fetuses, and neonates. Research on the pregnant must benefit either the mother or the fetus, or else risks to the fetus may be no more than minimal. Risks, of course, must always be minimized. Curiously, the party whose consent must be sought depends on the distribution of benefits. If the research will benefit the mother alone, both the fetus and the mother, or neither, then the mother's consent alone is enough. If the research will benefit only the fetus, then consent should be obtained from both the mother *and* the father (unless the father is unavailable). Cautions are made that termination of pregnancy cannot be bought, arranged, or performed by the researchers.

Guidelines for research on neonates are determined by whether the infant is viable, the infant is not viable, or viability is uncertain. For viable neonates, research is evaluated based on Subparts A and D of 46 CFR 45. Research on nonviable infants cannot include stopping vital signs, but neither can it artificially prolong them. Permission to involve a nonviable neonate in research should be given by both parents, but either parent can give consent if the other is unable. If viability is uncertain, research should be aimed at increasing the chance at viability. In this case, either parent may give consent. Of note, no member of the research team may make the initial decision regarding the viability of the newborn.

Prisoners

Subpart C of 46 CFR 45 was written to protect prisoners from exploitation while at the same time ensuring that they have a fair chance at participating in research. If an IRB is to evaluate potential research using prisoners as subjects, it must have a prisoner or prisoner advocate as a member. The research should not offer benefits unrelated to the experimental treatment because such benefits can become coercive to prisoners. Nor should research participation ever influence parole boards. The research should be open to all study-appropriate prisoners and not used to preferentially reward certain individuals. Finally, the research should be related to either criminal behavior/incarceration or problems that affect the prison population disproportionately (e.g., hepatitis or tuberculosis).

Children

Subpart D of 46 CFR 45 pertains to research with children. The major difference in research with children is that they are unable, by definition, to give consent. Therefore, assent is sought instead. Assent is defined in the policy as "a child's affirmative agreement to participate in research" (§46.402[b]). However, if the child is unable to provide assent given the child's "age, maturity, and psychological state" (§46.408[a]) and the research presents a unique beneficial opportunity for the child, assent may be waived. In all cases the child's legal guardian must give permission.

It is important to note that Subpart D contains a stratification of research-related risks. In addition to the minimal risk category, there are categories of "minor increase over minimal risk" (§46.406[a]) and more than a minor increase over minimal risk. All of these risk levels should be examined in the context of the anticipated benefit for the child involved. Research containing more than a minor increase over minimal risk—and without the possibility of benefit to the individual child enrolled—can be appealed to a "panel of experts in pertinent disciplines" (§46.407[b]). If the study seems to represent an opportunity to benefit children as a group, the study can be allowed.

Council for International Organizations of Medical Sciences Guidelines

The Council for International Organizations of Medical Sciences (CIOMS), a nongovernmental organization founded in 1949, was established to collaborate with the United Nations and its subgroups—such as the World Health Organization (WHO). After the WMA adopted the Declaration of Helsinki in 1964, the WHO directed CIOMS to translate the declaration into a document

that could be used to guide member countries—especially Third World countries. The CIOMS manual, *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects*, was released in 1982.

In response to the global HIV/AIDS crisis, CIOMS included new guidelines regarding multinational trials and the use of vulnerable populations. However, shortly after their release, an ethical controversy erupted that led to a second update.[13] At issue were studies sponsored by industrialized nations but which took place in the Third World. In these trials the participants in control arms got treatments that were not recognized as "established effective interventions" in the industrialized nation supporting the studies[13(p5)] (for more reading on this controversy, see [14–17]). The argument came down to using the standard of care in the Third World country to investigate the most cost-effective way of treating HIV/AIDS in low-resource countries versus industrialized countries exploiting the Third World to get studies done that could not be done within their borders. Eventually, an update containing 21 guidelines was published in 2002—without resolving the issue.

The first 3 guidelines require that a study be scientifically sound and approved by the appropriate IRB. In the case of researchers sponsoring studies in foreign countries, this includes having sponsors get approval from their own IRB—not just the host country's equivalent.

Guidelines 4 through 7 are concerned with informed consent. The information disclosed should include the voluntary nature of the study, the right to quit at any time, how the project differs from clinical care, terms like *blinding* and *randomization* as appropriate, the duration, compensation (including compensation for study-related injury/death), risks and benefits, the right to access the study results and the individual's data, steps to maintain privacy, and disclosure of sponsors/funding sources (see table 1). Only after the potential subject understands this information should consent be sought. In obtaining consent, the researcher or representative should "refrain from deception, undue influence, or intimidation."[13(p25)] Subjects can be compensated—but only within reason and not to bribe them into participation.

Guidelines 8 and 9 discuss the risks and benefits of studies. If there is no possible benefit to the individuals entering a study, risks "must be reasonable in relation to the importance of the knowledge to be gained."[13(p30)] If individuals entering a study cannot give informed consent and the research does not allow for the individuals involved to benefit, the risks can be "no more likely and no greater than the risk attached to routine medical or psychological examination of such persons."[13(p31)]

Guidelines 10 and 12 are designed to limit exploitative research in low-resource areas. Guideline 10 states that the research must be useful to the community in which it is carried out and that results must be made reasonably available to the community. Guideline 12 states that the "burdens and benefits" of research should be shared equitably within the community and globally.[13(p40)]

Guideline 11 is concerned with the choice of control interventions. According to the CIOMS, it is only ethical to use a placebo in 1 of 3 situations: when there is no established intervention, when withholding an intervention would only cause "temporary discomfort or delay in relief of symptoms," or when using placebo is scientifically necessary *and* would "not add any risk of serious or irreversible harm."[13(pp34–35)] (It is under Guideline 11's commentary that the controversy over HIV drug trials in Africa sponsored by institutions in the United States is discussed.)

Guideline 13 states that vulnerable populations should only participate in research under certain conditions. These conditions are set forth in Guidelines 14 and 15. Guideline 14 deals with pediatric research. Children can only be used as subjects if adults cannot be used, the research is "relevant to the health needs of children," the legal representative of the child consents, *and* the child provides continuous assent.[13(p43)] Guideline 15 pertains to the mentally ill. As with children, it states that people with psychiatric illness can only participate if the research is intended to benefit this population and cannot be carried out on people without mental illness. The mentally ill must also provide consent or assent as appropriate and, when not able to provide consent, have a legal guardian give permission.

Guidelines 16 and 17 concern women participating in research. Women should not automatically be excluded from research because of the possibility that they could become pregnant. Rather, the researchers should inform potential subjects of the study-related risks in becoming pregnant and offer pregnancy testing and "access to effective contraceptive methods before the research commences."[13(p47)] If a woman is pregnant, she may be included in research provided she is informed of risks, the research is relevant to the pregnancy, and animal models have previously examined teratogenic risk.

Guidelines 18 states that individual's data must be safeguarded as confidential. Guideline 19 makes the controversial claim that any injury resulting from the research must receive free medical care and that the individual must receive "financial or other" compensation.[13(p51)] On the occasion of a participant's death as a result of the research, the subject's survivors are entitled to such compensation. The remaining 2 guidelines are aimed at improving the quality of ethical review in the Third World and specifying that the above guidelines apply to sponsors and not just hosts of a project.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use's Guideline for Good Clinical Practice

Every industrialized country in which pharmaceuticals are manufactured has a regulatory system to ensure

that medications are appropriate for the public. Until recently, the ways in which these systems operated were all different. This led to redundant efforts to satisfy different regulations that, in turn, led to delays in getting new medications to the public. In 1990, the European Federation of Pharmaceutical Industries and Associations hosted a meeting in Brussels to discuss plans for the United States and Japan to join Europe in standardizing requirements for the approval of pharmaceuticals. After all, Europe was able to come to a "harmonized" policy despite varying languages and governments. Regulatory and industry representatives from the United States, Japan, and Europe agreed, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was created.

The major areas of harmonization are the areas on which approval of a new drug is based: safety, quality, and efficacy. Although the text of the harmonization documents spans hundreds of pages, the document most pertinent to this article is "The Guideline for Good Clinical Practice."

"The Guideline for Good Clinical Practice" (GCP) was released in 1996.[18] It was meant to reflect the "current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization."[18(p1)] The most relevant sections it contains are a section defining terms, a section enumerating the principles of good clinical practice, and a section on IRBs (see table 1 for elements of informed consent required by the GCP).

The glossary defines technical terms such as *blinding*, *protocol*, and *randomization*—however, it also defines terms involved in the practice of ethically sound research. The document describes IRBs but also what it calls "Independent Ethics Committees (IECs)." The IECs are a more general form of review committee. Whereas IRBs are, by definition, "institutional," IECs could be institutional, regional, national, or international. Therefore, IRBs are a specific type of IEC. Another definition worth examining is that of "vulnerable subjects." According to the GCP, vulnerable subjects are "individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate."[18(p9)] Interestingly, the list of vulnerable people does not mention psychiatric patients per se at all. The groups mentioned are health profession trainees, health industry employees, the military, prisoners, the chronically ill, the terminally ill, residents of nursing homes, the impoverished, emergency patients, ethnic minority groups, minors, and "those incapable of giving consent."[18(p9)] Although psychiatric patients may fit into more than 1 above category, it is important to note that psychiatric patients were not singled out for mention in the definition any more than individuals with diabetes were.

The second section of the GCP document is an actual enumeration of what constitutes good clinical practice. The section starts by saying that research should be done using the principles that have come from the Declaration of Helsinki (although the principles underlying the declaration are older than the declaration itself and, arguably, do not owe their origin to that specific document). Additionally, a study can occur only if the potential benefits outweigh the risks—"the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society."[18(p9)] Before a trial can be conducted, the product to be investigated must have been through adequate nonclinical testing. A trial should be conducted in a manner approved by the relevant IRB/IEC. The medical care of each subject must be overseen by a competent physician, and all members of the project must be qualified for their roles. Informed consent should be obtained. Clinical data should be "recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification."[18(p9)] Identifying information should be kept confidential. Finally, any product tested should be made and managed according to "applicable good manufacturing practice."[18(p9)]

The section on IRBs/IECs describes group membership similar to the Common Rule (at least 5 members, 1 independent of the institution, etc). However, it defines the duties of the group in more detail than the Common Rule. The IRB/IEC is charged to "safeguard the rights, safety, and well-being of all trial subjects."[18(p9)] The group should also verify that the investigator is qualified for the project. It should periodically review the study for safety—at least once per year. It ensures the ethical treatment of subjects when they require surrogate consent or when, due to an emergency, there is no informed consent. Finally, the IRB/IEC examines what payment will be given in order to rule out coercion. In fact, "the IRB/IEC should ensure that information regarding payment to subjects … is set forth in the written informed consent."[18(p10)]

National Bioethics Advisory Commission Report

The National Bioethics Advisory Commission (NBAC) was created through executive order by President Clinton in 1995. One of the assignments of the commission was to advise the U.S. government on gaps in federal protections for vulnerable populations participating in research. The commission saw such a gap in protections for the mentally ill. Its report consists of an 88-page volume of recommendations (released in 1998) and a 78-page volume of commissioned papers on the subject (released in 1999) collectively titled *Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity*.[19]

The report makes 21 recommendations targeted to 6 areas.

Research Design

- People with mental illness should not be subjects when the study does not require this patient population.
- Research designs should minimize risks (including use of placebos and symptom provocation—although these techniques are not disallowed).
- A "thorough" report of risks and benefits should be provided to the IRB.[19(piv)]

Informed Consent and Capacity

- If individuals have the capacity to provide consent, they *must* do so before participating in a trial.
- Disregarding capacity to consent, *any* subject's objection to enrollment or continued participation must be obeyed.
- Potential subjects must be evaluated for capacity to consent when a protocol entails greater than minimal risk. The evaluator should be independent of the project, but the formality of the evaluation depends upon the IRB.
- If an individual is determined incapable of consent, he or she must be advised of this before a legally authorized representative (LAR) is sought for permission to enroll a patient. (In all cases the patient must still assent to participation.)

Surrogate Decision Making

- A patient may give "prospective authorization" for a type of research. Later, when the patient becomes unable to consent, the LAR may enroll the patient in this type of research. The LAR should oversee the patient's experience during the study.
- The LAR must make decisions based on the best interest of the patient.
- The LAR may be an interested party who was not formally appointed by the patient and may act in the absence of a prospective authorization (just as a clinical surrogate decision maker acts).
- States should legislate a patient's ability to choose his or her own LAR.
- In cases of people with "fluctuating or limited decision-making capacity or prospective incapacity," researchers should maintain contact with important people in the person's life.[19(pvi)]

Education, Research, and Support

- Professional groups should educate others about mental illness research.
- Research on decision-making capacity should be encouraged and supported.
- A more detailed examination of the risks to decision-making capacity posed by "challenge, washout, and placebo controlled studies" is needed.[19(pvii)]
- Governments, universities, and private industry should provide resources to comply with these recommendations.

Review Bodies

- IRBs should include at least 2 individuals with experience in mental disorders (1 of whom must be an individual with a mental disorder, a family member, or a patient advocate) whenever a protocol involving this population comes up.
- A Special Standing Panel (SSP) should be created by the DHHS to evaluate projects that do not conform to the above recommendations. The SSP may approve these projects if the potential benefit to the population being studied is "substantial" and risks are "reasonable."[19(piii)]

Categories of Research

- In studies involving minimal risk, patients may enter a study if consent has been waived by the IRB, informed consent is obtained, or the LAR gives permission (and the patient agrees).
- In studies involving a greater risk but also direct benefit, patients may enter a study if informed consent is obtained or the LAR gives permission (and the patient agrees).
- In studies involving greater risk and little direct patient benefit, patients may enter a study if informed consent is obtained, the patient has specified that he or she wishes to participate in this type of study (by prospective authorization) and the LAR gives permission, or by virtue of approval by the SSP.

Critiques

Although the NBAC's interest in protecting this population was almost universally applauded, there were several critiques of the recommendations. Most notable is the observation that research involving mentally ill people was only divided into "minimal risk" and "greater than minimal risk"—without a "minor increase over minimal risk" category (as was established for children in Subpart D of 45 CFR 46—see the section on the Common Rule above).[20–21] Potential subjects in any study with greater than minimal risk must be evaluated for capacity to consent. If potential enrollees in such a study are unable to consent, the study must be evaluated by the SSP. Oldham et al. postulate that this would significantly obstruct research into mental illness—especially as there would be only a single SSP for the entire country.[20]

Table 2. Examples Illustrating Differences in Ethical Codes

Document	Example Studies		
	Placebo for Cognition Allowed?	Placebo for Psychosis Allowed?	Symptom Provocation Allowed?
Nuremberg Code	Yes	Yes	Yes
Declaration of Helsinki	Yes	No—known treatments exist	No—study not intended to treat, prophylax, or diagnose
Belmont Report	Yes	Yes	Yes
Common Rule	Yes	Yes	Yes
Council for International Organizations of Medical Sciences Guidelines	Yes	No—known treatments exist	Yes
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use "Guideline for Good Clinical Practice"	Yes	Yes	N/A

Additionally, the possibility of subtle stigmatization has been raised.[20] By requiring any potential subject considering a study with greater than minimal risk to undergo an evaluation of capacity to consent, the implication is that a person with mental illness is assumed incapable of consent unless proven otherwise (whereas in a person without mental illness the reverse is true).[21] The report itself points out that problems in decision making are not unique to people with mental illness but, indeed, are present in a variety of more "medical" illnesses (e.g., AIDS, cancer, delirium, and dementia)—yet the report is focused on mental illness and not generally on people whose decision-making ability may be compromised.

Conclusion and Examples

After examining the above documents, 2 things become obvious. First, there is remarkable agreement spanning several decades of thought on what constitutes ethical research. Second, despite this general agreement, there are still significant areas where the most important ethical guidelines differ. These differences should only spur further empirical and reflective work on the subject—such as suggested by the NBAC report.[19] To highlight differences in the major codes reviewed (Nuremberg, the Declaration of Helsinki, the Common Rule, CIOMS guidelines, and the ICH "Guideline for Good Clinical Practice"), the next sections describe 3 examples of schizophrenia research projects and what the various codes would say about them (see also table 2).

Example 1

The first example is of a placebo-controlled study to examine whether Drug X is effective in enhancing cognition in people with schizophrenia. The study is funded by a U.S. government grant, headed by psychiatrists and psychologists from a U.S. university, and will take place with patients who are U.S. citizens. Drug X has been tested in animals and preliminarily in humans and does not seem to present any danger of death or disability. The main issues that would require examination would be the involvement of people with schizophrenia and the use of placebo.

As far as involving people with schizophrenia, it would depend on the subjects' ability to provide consent. If they are able to do so, none of the codes involved would prohibit the study solely on the grounds of the patient population. In fact, research has shown that the mere diagnosis of schizophrenia does not automatically imply incompetence.[22–27] The use of placebo in this situation would be allowed by any of the ethical codes examined because, at the moment, there is no recognized treatment for the cognitive disabilities associated with schizophrenia. Therefore, it seems that none of the ethical codes examined would, prima facie, prohibit this study.

Example 2

The second example is the same as the first in every respect save that the researchers want to study a new antipsychotic versus a placebo. In this case some of the codes examined would not allow the study because there is a rather large number of recognized effective treatments for psychosis; therefore, a placebo study should not occur. Other codes would allow the study as long as certain conditions were met.

The Declaration of Helsinki would not allow such a study to be done because the condition being investigated, psychosis related to schizophrenia, is not minor and using a placebo entails additional risk to the

patient. Nor is the use of placebo absolutely required to assess the new drug's effectiveness. Following suit, the CIOMS guidelines would also prohibit such a study. Additionally, the study results could not be published according to the Vancouver Group's proscription of studies not conducted according to the Declaration of Helsinki.

On the other hand, the ICH's GCP document allows a broader range of placebo use and would not automatically prohibit the study. Neither would the Belmont Report or the federal Common Rule. These documents would encourage an examination of the study's safety and design and the information presented to potential recruits before making a decision. Of particular concern would be how much risk is entailed by withdrawing antipsychotic medication in the context of the research setting. (For a discussion of this topic, see [28–38].)

Example 3

The third example is the use of Compound Z in pharmacologic challenge studies to increase positive symptoms and examine a possible mechanism of their production in people with schizophrenia. Again, the Declaration of Helsinki would have problems with the study; in this case because the study is not intended to prophylax, diagnose, or treat. However, the CIOMS would at least allow consideration of the study as long as the risks were "reasonable in relation to the importance of the knowledge to be gained."[13(p30)] The Belmont Report and federal Common Rule would also weigh the risks and benefits before deciding whether the study was allowable. Under the CIOMS guidelines and the federal Common Rule, the researchers would have to establish the risk of symptom provocation and the potential benefit for schizophrenia research presented by the study. (For a discussion on symptom provocation, see [39–41].) Note that the ICH "Guideline for Good Clinical Practice" is for research on potential treatments and so does not apply to this example.

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References

1. Harris S. Japanese biological warfare research on humans: a case study of microbiology and ethics. *Ann NY Acad Sci* 1992;666:21–52.
2. Annas GJ, Grodin MA. *The Nazi Doctors and the Nuremberg Code*. New York: Oxford University Press; 1992.
3. World Medical Association. *Ethical Principles for Medical Research Involving Human Subjects (aka the Declaration of Helsinki)*. 2004. Available at www.wma.net.
4. Carpenter WT, Jr., Appelbaum PS, Levine RJ. The Declaration of Helsinki and clinical trials: a focus on placebo controlled trials in schizophrenia. *Am J Psychiat* 2003;160: 356–362.
5. Brennan TA. Proposed revisions to the Declaration of Helsinki—will they weaken the ethical principles underlying human research? *N Engl J Med* 1999;341(7):527–531.
6. Levine RJ. The need to revise the Declaration of Helsinki. *N Engl J Med* 1999;341(7):531–534.
7. Appelbaum PS. Drug-free research in schizophrenia: an overview of the controversy. *IRB: Rev Hum Subj Res* 1996; 18(1):1–5.
8. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med* 1994;331:394–398.
9. Beecher HK. Ethics and clinical research. *N Engl J Med* 1966;274(24):1354–1360.
10. International Committee of Medical Journal Editors (aka the Vancouver Group). *Uniform Requirements for Writing Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication.* 2004. Available at www.icmje.org.
11. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Ethical Principles and Guidelines for the Protection of Human Subjects of Research (aka the Belmont Report)*. 1979. Available at http://ohsr.od.nih.gov/guidelines/belmont.html.
12. Department of Health and Human Services, National Institutes of Health, Office for Protection from Research Risks. *Title 45: Public Welfare, Part 46: Protection of Human Subjects (aka the Common Rule)*. 2001. Available at www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.
13. Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. 2002. Available at www.cioms.ch.
14. Angell M. The ethics of clinical research in the Third World. *N Engl J Med* 1997;337(12):847–849.
15. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *N Engl J Med* 1997;337(12): 853–856.
16. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Engl J Med* 1997;337(14): 1003–1005.
17. Cohen J. Ethics of AZT studies in poorer countries attacked. *Science* 1997;276:1022.
18. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Steering Committee. *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice (E6)*. 1996. Available at www.ich.org.
19. National Bioethics Advisory Commission. *Research Involving Persons With Mental Disorders That May Affect Decision-making Capacity*. 1998. Available at www.georgetown.edu/research/nrcbl/nbac/capacity/TOC.htm.
20. Oldham JM, Haimowitz S, Delano SJ. Protection of persons with mental disorders from research risk. *Arch Gen Psychiat* 1999;56(8):688–693.
21. Meslin EM. The National Bioethics Advisory Commission (NBAC) report [commentary]. *Biol Psychiat* 1999;46(8): 1011–1012.
22. Moser DJ, Reese RL, Schultz SK, et al. Informed consent in medication-free schizophrenia research. *Am J Psychiat* 2005; 162(6):1209–1211.

23. Jeste DV, Dunn LB, Palmer BW, et al. A collaborative model for research on decisional capacity and informed consent in older patients with schizophrenia: bioethics unit of a geriatric psychiatry intervention research center. *Psychopharmacology* 2003;171(1):68–74.
24. Moser DJ, Schultz SK, Arndt S, et al. Capacity to provide informed consent for participation in schizophrenia and HIV research. *Am J Psychiat* 2002;159(7):1201–1207.
25. Dunn LB, Lindamer LA, Palmer BW, Golshan S, Schneiderman LJ, Jeste DV. Improving understanding of research consent in middle-aged and elderly patients with psychotic disorders. *Am J Geriat Psychiat* 2002;10(2):142–150.
26. Grisso T, Appelbaum PS. Comparison of standards for assessing patients' capacities to make treatment decisions. *Am J Psychiat* 1995;152(7):1033–1037.
27. Grisso T, Appelbaum PS. The MacArthur Treatment Competence Study: III. abilities of patients to consent to psychiatric and medical treatments. *Law Human Behav* 1995;19: 149–174.
28. van de Laar N, Henter I, Bartko JJ, Wyatt RJ. Adverse events during a placebo phase for inpatients with chronic schizophrenia. *Biol Psychiat* 2001;50:487–492.
29. Johnstone EC, Owens DGC, Crow TJ, Davis JM. Does a four-week delay in the introduction of medication alter the course of functional psychosis? *J Psychopharmacol* 1999;13:238–244.
30. Wyatt RJ, Henter I, Bartko JJ. The long-term effects of placebo in patients with chronic schizophrenia. *Biol Psychiat* 1999;46:1092–1105.
31. Weijer C. Placebo-controlled trials in schizophrenia: are they ethical? are they necessary? *Schizophr Res* 1998;35:211–218.
32. Zipursky RB, Darby P. Placebo-controlled studies in schizophrenia—ethical and scientific perspectives: an overview of conference proceedings. *Schizophr Res* 1999;35:189–200.
33. Streiner DL. Placebo-controlled trials: when are they needed? *Schizophr Res* 1999;35:201–210.
34. Carpenter WT, Jr., Schooler NR, Kane JM. The rationale and ethics of medication-free research in schizophrenia. *Arch Gen Psychiat* 1997;54(5):401–407.
35. Carpenter WT, Jr. The risk of medication-free research. *Schizophrenia Bull* 1997;23:11–18.
36. Lehrman NS, Sharav VH. Ethical problems in psychiatric research. *J Ment Health Admin* 1997;24:227–250.
37. Miller FG, Rosenstein DL. Psychiatric symptom-provoking studies: an ethical appraisal. *Biol Psychiat* 1997;42:403–409.
38. Gilbert PL, Harris MJ, McAdams LA, Jeste DV. Neuroleptic withdrawal in schizophrenic patients. *Arch Gen Psychiat* 1995;52:173–188.
39. Avila MT, Conley RR, Carpenter WT, Jr. A comparison of symptom provocation procedures in psychiatry and other areas of medicine: implications for their ethical use in research. *Biol Psychiat* 2001;50:479–486.
40. D'Souza DC, Berman RM, Krystal JH, Charney DS. Symptom provocation studies in psychiatric disorders: scientific value, risks, and future. *Biol Psychiat* 1999;46:1060–1080.
41. Carpenter WT, Jr. The schizophrenia ketamine challenge study debate. *Biol Psychiat* 1999;46(8):1081–1091.

Appendix. Web Addresses for Documents Discussed

Document	Web Address
Declaration of Helsinki	www.wma.net
Vancouver Group's *Uniform Requirements*	www.icmje.org
Belmont Report	www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
(U.S.) Common Rule	www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
Council for International Organizations of Medical Sciences Guidelines	www.cioms.ch
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use "Guideline for Good Clinical Practice"	www.ich.org
National Bioethics Advisory Commission Report	www.georgetown.edu/research/nrcbl/nbac/capacity/TOC.htm